

The Office Action cites case law where evidence involving a single compound and two types of cancer was held insufficient to establish the utility of claims directed to a method of treating two cancers. As noted above, Applicants have presented evidence relating to numerous compounds and 9 cell lines corresponding to 9 types of cancer. The application contains 35 examples.

Referring to Table 2 of the application, the effect of PBOX compounds on apoptosis in HL-60 cells is shown. For example, PBOX 6 is found to induce $38.6 \pm 4.6\%$ apoptosis in HL-60 cells. Applicants previously submitted a supplementary table of results which demonstrate the ability of the claimed compounds to induce apoptosis in additional exemplary cell lines, such as prostate cancer (PC3) and ovarian carcinoma (OAW42). That data was provided in support of Applicants' argument that claims 40-42 are fully enabled. That data shows that treatment of prostate cancer cells (PC3) with $10\mu\text{M}$ PBOX 6 for 16 hours (i.e., similar conditions to those used in Table 2 of the present application) induced 39% apoptosis. As indicated earlier, Applicants would be pleased to provide a Declaration which attests to the noted data should it be required.

In further support of their arguments, Applicants previously filed a journal article entitled "Tumor selective G₂/M cell cycle arrest and apoptosis of epithelial and hematological malignancies by BBL22, a benzazepine" (Xia et al., *PNAS*, June 20, 2000, vol. 97, no. 13, pp. 7494-7499). This paper describes a PBR ligand, BBL22, which induces arrest in the G₂/M phase of the cell cycles in human tumor cell lines of both epithelial and hematopoietic cellular origin. In particular, this reference teaches that several tumor types, notably prostate and certain breast cancer cell lines, exhibit significant apoptosis when treated with BBL22.

In view of the foregoing, clearly the skilled artisan would readily understand that the present invention describes and is indicative of how the claimed compounds would behave in the body. As such, the full scope of claims 40-42 is enabled. In summary, it is submitted


that the present application together with the knowledge possessed by one skilled in the art provide ample enablement for claims 40-42.

Reconsideration and withdrawal of the rejection are thus requested.

Applicants request that the Examiner telephone the undersigned attorney in order to schedule a telephonic interview on these issues prior to issuance of a further Office Action.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



Christine C. O'Day
(Reg. No.: 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. (617) 439-4444

VERSION MARKED TO SHOW CHANGES

IN THE CLAIMS:

The following new claim was added:

48. A method of claim 45 wherein the compound is selected from the group consisting of:

4-Acetoxy-5-phenylnaphto[2,3-b]pyrrolo[1,2-d][1,4]oxazepine,
7-Acetoxy-6-(1-naphthyl)pyrrolo[2,1-d][1,5]benzoxazepine,
4-[(Dimethylcarbamoyl)oxy]-5-phenylnaphto[2,3-b]pyrrolo[1,2-d][1,4]oxazepine,
7-[(Dimethylcarbamoyl)oxy]-6-(1-naphthyl)pyrrolo[2,1-d][1,5]benzoxazepine,
7-[(Methylcarbamoyl)oxy]-6-(1-naphthyl)pyrrolo[2,1-d][1,5]-benzoxazepine,
7-[(Dimethylcarbamoyl)oxy]-6-(1-naphthyl)pyrrolo[2,1-d][1,5]benzothiazepine,
7-Acetoxy-6-(1-naphthyl)pyrrolo[2,1-d][1,5]benzothiazepine,
7-Acetoxy-6-(1-naphthyl)pyrrolo[1,2-d]pyrido[3,2-b][1,4]oxazepine,
4-Acetoxy-5-(1-naphthyl)naphtho[2,3-b]pyrrolo[1,2-d][1,4]oxazepine,
4-[(Dimethylcarbamoyl)oxy]-5-(1-naphthyl)naphtho[2,3-b]pyrrolo[1,2-d][1,4] oxazepine, 7-
[(Ethylcarbamoyl)oxy]-6-phenylpyrrolo[2,1-d][1,5]benzoxazepine,
7-[(Methylcarbamoyl)oxy]-6-phenylpyrrolo[2,1-d][1,5]benzoxazepine,
7-Isonicotinoyloxy-6-(p-methoxyphenyl)pyrrolo[2,1-d][1,5]benzothiazepine,
7-(Butyryloxy)-6-(p-methoxyphenyl)pyrrolo[2,1-d][1,5]benzothiazepine 5-Oxide.